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MICROBIAL ECOLOGY OF CHILDHOOD ASTHMA: DECIPHERING THE INTERPLAY AMONG MICROBIOTA, ALLERGENS, AND HOST DEFENSE

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ABSTRACT
The burden of Paediatric asthma, a chronic respiratory illness with an alarming increase in its occurrence, affects millions of children. The development and exacerbation of asthma are closely associated with the dysbiosis of the airway microbiota, environmental allergens, and host immunity. The interplay between microbiota, environmental allergens, host immunity and dysbiosis of the airway microbiota is a critical area of research in the pathogenesis and progression of childhood asthma. Novel therapeutic interventions such as microbiome-based therapies or personalized immunomodulatory treatments ought to be developed. We investigate the possibilities of such therapeutic interventions, targeting the microbiota's dysbiosis and the immune system's dysregulation, which will certainly lead to more effective treatment and management of childhood asthma. The present review article attempts to explore the interplay between microbiota, environmental allergens, and host immunity in the development of childhood asthma, while highlighting the importance of probiotics, prebiotics, and immunomodulatory drugs in modulating the microbiome which improves asthma outcomes. The article also elaborates on the recent findings and potential future directions of innovative research and therapeutic interventions.
KEYWORDS: Asthma, Allergens, Host immunity, Microbiome, Microbiota, Immunomodulation.

INTRODUCTION
Asthma is a lung disorder leading to airway inflammation and narrowing, causing dyspnea (1). Asthma symptoms vary from individual to individual; some frequent signs include coughing, wheezing, difficulty in breathing, and chest heaviness. These symptoms are caused by factors like environmental changes, including allergens, air pollution, respiratory infections, and emotional stress(2). “Asthma is a heterogeneous disease defined by the history of respiratory symptoms (e.g., wheeze, shortness of breath, chest tightness, and cough) that vary over time and in intensity, together with variable expiratory airflow limitation”(3). This recent definition of asthma identifies it as a disorder caused by long-term inflammation of the respiratory tract and varying degrees of air flow blockage. Environmental triggers such as allergens, air pollution, respiratory infections, and emotional stress are just a few examples (4). The complex etiology and the atypical symptoms in the early stages make it challenging to diagnose and manage asthma effectively (5-7)

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In India, asthma is a chief public health issue, affecting millions of population across the nation. The prevalence of asthma varies across different regions and populations, with some studies reporting rates as high as 13.7% among adolescent children. Asthma can affect the quality of life, leading to long absence in school or workplace. The management and treatment of asthma involves a combination of medication and lifestyle changes. Inhaled corticosteroids are commonly used to reduce inflammation in the airways, while bronchodilators can help relax the muscles around the airways and improve breathing. Avoiding triggers such as allergens or air pollution can also help manage asthma symptoms. In addition, lifestyle changes such as maintaining a healthy weight and avoiding smoking can reduce the risk of asthma exacerbations.

Asthma is a complex condition with potential causes and triggers. The advancement of asthma is triggered by external components like air pollution and exposure to various allergens. In addition, genetic factors also cause development of asthma, as the condition often runs in families. Lifestyle factors, such as morbid obesity and tobacco usage are associated with an increased likelihood of developing asthma. Diagnosing asthma involves a multifaceted approach with a combination of clinical examinations and pulmonary function tests.

Millions of children across the world, suffer from this chronic respiratory condition of childhood asthma. Global Asthma Report 2022 predicts that by the year 2025, there will be 400 million people suffering from asthma worldwide against the 262 million in 2019. This is a pressing issue in India, as approximately 35 million people suffer from the chronic respiratory condition (8). A recent meta-analysis conducted on a large sample size of children, revealed that the estimated burden of asthma in India was nearly 8%(9). Several studies point towards varying prevalence rates of childhood asthma in India, across different age groups and different study periods. Among the children who come under 6 to 14 age group, the prevalence rate ranges from 2.4% to 13.7%(10-12).

Besides diet and physical activity, risk factors for childhood asthma include family history, environmental factors such as air pollution and pollens (14). Children with a familial background of asthma or allergies, are seen to be more prone towards developing asthma (15). Other environmental factors such as pollutants in the air, second hand smoking and allergens, along with behavioral factors such as obesity and sedentary lifestyle are correlated with enhanced likelihood of developing asthma (16).

Human microbiota and airway microbiota

The human microbiota, consisting of billions of microorganisms, has an important role in maintaining health. These microorganisms are involved in a range of essential physiological processes such as digestion, metabolism, and immune function. The composition of the microbiota varies depending upon age, food intake and environmental exposures. The changes in the microbiota composition are associated with several diseases including asthma (17). The population of microbes living in the respiratory system is known as the *airway microbiota*. These microbes determine how well an asthma patient responds to treatment and play an important role in preserving the health of the respiratory system.

The potential link between microbial imbalance and childhood asthma has become an area of increasing research interest. Recent studies suggest that intestinal microbiota alterations and respiratory microbiota too play a part in the development and progression of asthma, and environmental factors may interact with the microbiota to influence asthma risk(18).

For a comprehensive understanding of the intricate pathophysiology of asthma, it is crucial to explore how the microbiota, environmental allergens, and host immunity interact with each other. Disturbance in the normal equilibrium of the microbiota is linked to an increased susceptibility to asthma, while exposure to environmental allergens triggers a cascade of immune responses that leads to asthma exacerbation(19).

The intestinal and respiratory microbiota has a critical role in controlling the immune responses to environmental allergens (20). Therefore, understanding the interaction of all underlying factors can help develop newer therapeutic approaches for asthma management, such as microbiome-based interventions or personalized immunomodulatory therapies. The present paper explores the interaction between microbiota, environmental allergens, and host immunity in the pathogenesis of childhood asthma, focusing on recent findings while figuring out the potential plans for research and therapeutic interventions.

Airway microbiota and Asthma

The respiratory microbiota is a community of microorganisms that colonizes the respiratory tract and has a significant role in the progress of asthma because of its influence on the immune system (21, 22). Studies have shown that an imbalance in the respiratory microbiota (dysbiosis) can lead to the development or exacerbation of asthma (23, 24). Dysbiosis can cause alterations in immune function and impact the continuity of the respiratory epithelium, causing inflammation, tissue damage, and worsening of asthma symptoms(19).

"Changes in Airway Microbiota in Asthma"

Researches show that airway microbiota varies in individuals with and without asthma. Individuals with asthma have a decreased microbial diversity and an increased bacterial taxa, including Proteobacteria and Firmicutes(25). Exposure to environmental factors can exacerbate changes in the composition and quantity of airway microbiota in children who have asthma. This microbiota can influence immune responses in the respiratory system, potentially causing immune dysfunction thereby elevating the risk of developing asthma (26). Incidentally, the airway microbiota can impact the generation of mucus and the configuration of the airway's epithelial lining, leading to the onset of asthma (27).

Children who have asthma, display varying microbiota compositions in their respiratory tracts, as compared to those without asthma. This disparity includes the excessive growth of certain bacterial species like "Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis" (7). These microbes are known to trigger immune reactions, leading to airway inflammation and worsening of asthma symptoms. Children diagnosed with asthma tend to have a decreased variety of microorganisms and an elevated presence of potentially pathogenic bacteria (20). These bacteria can induce inflammation and contribute to airway obstruction in children with asthma(28).

Table 1: Overview of Studies on Microbiota and Childhood Asthma with Effect Sizes

Study	Sample Size	Effect Size	Findings
Bisgaard *et al.*, 2007(29)	321	-	Cases with asthma have decreased bacterial diversity in their respiratory epithelium as compared to normal controls.
Marri *et al.*, 2013(30)	39	+	Increased concentrations of Proteobacteria and decreased Firmicutes in their respiratory tracts of cases with asthma.
Teo *et al.*, 2015(31)	234	-	"Reduced bacterial diversity in early infancy was linked to a higher risk of developing asthma later"
Arrieta *et al.*, 2018(32)	319	+	"Children with asthma have higher levels of Veillonella and decreased levels of Faecalibacterium in their airways"

Study	Sample Size	Effect Size	Findings
Toivonen 2020 (6)	720	+	Modifying the microbiota in early childhood could be an effective primary prevention strategy for childhood asthma.

"+" indicates a positive effect size, meaning an increase in the measured parameter is associated with asthma; "-" indicates a negative effect size, meaning a decrease in the measured parameter is associated with asthma.

Understanding Host Immune Responses to Pathogens

The airway microbiota is an essential component that contributes to childhood asthma pathogenesis, through its influence on the immune system of the host (33). Dysbiosis of the airway microbial environment can lead to inflammation, tissue damage, and exacerbation of asthma symptoms(34). The immune system in children with asthma is often hyper reactive, leading to elevation of pro-inflammatory cytokines, that will eventually promote Th2-type immune responses(35). The airway microbiota releases by-products such as SCFAs (short-chain fatty acids) and lipopolysaccharides which modulates immune response (36).

The appropriate synthesis and regulation of immune cells on the surface level is crucial for the pathogenesis and exacerbation of childhood asthma(5). When there is a disturbance in the immune response in the airway mucosal surfaces, it causes immune dysfunction, inflammation, and tissue damage, which results in the development or worsening of asthma. This can activate epithelial cells and Mucosa-associated lymphoid tissue (MALT) that causes excess pro-inflammatory cytokines and further the recruitment and stimulation of immune cells, namely Th2 cells and eosinophils (37). These cells cause airway inflammation and hyperresponsiveness, both of which are characteristic features of asthma(38).

Apart from this, the breakdown of immune tolerance mechanisms in the superficial layer of immune cells can also lead to the pathogenesis of asthma. Defects in regulatory T cells within MALT can cause loss of tolerance to harmless antigens like allergens and commensal bacteria, leading to exaggerated immune responses and progression of allergic asthma (39).

Table 1 shows a summary of four remarkable studies that explored the relationship between respiratory microbiota and asthma (Bisgaard et al. (2007) found that asthmatic children had decreased bacterial diversity in their airways when compared to healthy children. According to Marri et al. (2013), children with asthma exhibited “elevated levels of Proteobacteria and reduced levels of Firmicutes” in their airways. Research conducted by Teo et al. (2015), observed that a reduction in bacterial diversity during early infancy was linked to a greater probability of developing asthma in adult life. Moreover Arrieta et al. (2018) discovered that children with asthma exhibited elevated levels of Veillonella and reduced levels of Faecalibacterium in their airways. Toivonen (2020) suggests that the interventions aimed at modifying the microbiota in early childhood, such as probiotics or prebiotics, may help to prevent the occurrence of asthma (6). The available evidence suggests a potential link between the airway microbiota composition and the development of childhood asthma.

Response to Asthma Treatment

The airway microbiota can also influence the response to asthma treatment. Children who respond well to inhaled corticosteroids have a higher abundance of Actinobacteria in their airways(40). Because of these findings, the airway microbiota may hold promise as a target for future asthma treatments. There is a growing interest in microbiota-based therapies for the treatment of asthma. These therapies include probiotics, prebiotics, and transplantation of fecal microbiota. Probiotics are living microorganisms which, when ingested, can offer advantages for one's health. “Prebiotics are compounds that encourage the proliferation of helpful bacteria in the digestive system” (41). To restore a healthy equilibrium of gut bacteria, fecal microbiota transplantation involves transferring stool from a healthy individual to the gut of the recipient. (42). More evidence is required to determine the safety and impact of these microbiota-based therapies for the treatment of asthma.

Probiotics are beneficial microorganisms, having a beneficial impact on health. They have been studied extensively for their potential ability to alter the intestinal microbiome and immune system of the individual. Probiotics are associated with decreasing inflammation of the airways, augmenting pulmonary function, and decreasing asthma symptoms in children. Lactobacillus rhamnosus is a type of probiotic which exhibits immunomodulatory effects in certain allergic diseases. Various research studies have investigated how probiotics can modify the production of cytokines in the intestine and related immune cells. Experimental studies in mouse model reported that administering oral Lactobacillus rhamnosus prior to allergic sensitization, reduces airway inflammation and hyperreactivity in children with asthma (43). Another systematic review stated that administering probiotics prenatally, especially in high-risk infants, gave promising effects in mitigating the onset of allergies in infants,

Yet another noteworthy review found probiotics supplementation to be beneficial in reducing the episodes of asthma and reducing IL-4 levels while increasing interferon-γ levels in children with the disease. No substantial effects were seen on other measures such as clinical or pulmonary tests (45). More research is essential to understand the prospective advantages of probiotics supplementation, in cases of childhood asthma.

Prebiotics are part of food that cannot be digested but helps in the growth of beneficial organisms in the intestine. Studies conducted in animals and human beings prove that prebiotics can alter the microbial flora of intestine and enhance immunity (46). In children with asthma, prebiotics helps to decrease airway inflammation and improve pulmonary function (47). However, the optimal types and doses of prebiotics for childhood asthma are still under investigation.

Immunomodulatory drugs modulate the immune system's response. They have been used in the treatment of asthma and several immune-mediated diseases. In childhood asthma, immunomodulatory drugs such as omalizumab, mepolizumab, and benralizumab have been found to be effective in lowering inflammation of the airways, enhance pulmonary function, and decrease the incidence of exacerbations(13). However, these drugs are expensive and may not be accessible to all patients.

Apart from these targeted interventions, lifestyle modifications such as reducing exposure to environmental triggers like air pollution and allergens can also improve asthma outcome. A recent meta-analysis found reducing indoor air pollution and implementing allergen avoidance measures improved asthma outcome in children (26).

Research in developing novel treatment strategies, for dealing with childhood asthma that focuses on the microbiome and the host's immunity is progressing. Probiotics, prebiotics, and immunomodulatory drugs show promising results in improving asthma outcomes. More research is to be done to determine the optimal regimens and recognize the potential risks and benefits. Apart from the targeted interventions, lifestyle modifications such as reducing exposure to environmental triggers can also improve asthma outcomes.

Role of Gut Microbiota in the Development of Childhood Asthma

Evidence shows that changes in the gut microbiota, could potentially induce onset of asthma in children. An imbalance in the equilibrium of gut and respiratory microbiota causes dysbiosis, which can be a potential contributor to the emergence of asthma (18). Besides, the airway microbiota can influence immune function, mucus production, and airway epithelium structure, leading to asthma development.

"Role of Gut Microbiota in the Development of Childhood Asthma"

Mechanism: The immune responses controlled by the gut microbiota, causes dysregulation of immunity and an augmented risk of asthma.

Table 2: Types of Microbes Involved in Asthma Trigger and Mechanism

Study Year	Age Range	Sample Size	Prevalence of Childhood Asthma
Stockholm 2018 (48)	5 years	690	At the age of one year, children with asthma had a declined level of "Roseburia, Alistipes", and Flavonifractor and increased strains of "Veillonella" compared to the control. Prevalence was 9%
Depner *et al.*, 2020 (49)	Infancy	720	The prevalence of asthma among infants of 2 months was 9%, and infants with asthma had lower levels of EMA. Children diagnosed with asthma are found to exhibit elevated levels of Bacteroides and Parabacteroides, raised levels of Enterococcus in comparison to those without the condition.
Patrick *et al.*, 2020 (50)	5 years	917	At the age of one year, children with increased α-diversity (Chao1 index) had lesser chance of developing asthma (OR 0·68 [0·46–0·99]; p=0·046) as compared to those without, suggesting that having a higher α-diversity was found to protective against asthma in 11% of children.
Boutin *et al.*, 2020 (51)	1 year	837	"21% of the infants studied had recurrent wheeze; those with both recurrent wheeze and atopic wheeze had lower α-diversity when they are 3 months old than others without these conditions. Increased α-diversity at 3rd month was linked to a lower risk of recurrent wheeze (OR 0·75 [0·6–0·95]; p=0·007)"

Four remarkable studies were conducted to investigate the burden of childhood asthma in different age groups and sample sizes. The Stockholm study, conducted in 2018 with a sample size of 690 children aged between 4-5 years, found that 9% of children developed asthma, and those with asthma had lower levels of Roseburia, Alistipes, and Flavonifractor, but higher levels of Veillonella at the completion of one year. The Depner et.al study, conducted in 2020 with a sample size of 720 infants, found that 9% of children developed asthma, and those with asthma had lower levels of Bacteroides and Parabacteroides, but higher levels of Enterococcus when 12 months old, as when compared to children without asthma. In a 2020 study by Patrick *et al.*, a sample of 917 children aged 6 years were taken. The study found that 11% of the children developed asthma. Furthermore, it was observed that children with asthma had lower α-diversity at the age of one, when compared to children without asthma. Increased α-diversity at the age of one was found to be protective against the development of asthma. Finally, the Boutin et.al study, conducted in 2020 with a sample size of 837 infants aged 1 year, found that 21% of them had recurrent wheeze.

Children who experienced frequent and atopic wheezing, had a lower level of α-diversity when they were 3 months old, as compared to those without these conditions. Conversely, a higher level of α-diversity at the third month was found to be linked with a decreased incidence of recurrent wheezing.

Certain types of gut bacteria, such as Bifidobacterium and Lactobacillus, can have a protective effect against asthma (52). These bacteria can produce metabolites that have anti-inflammatory properties and can modulate immune responses. In contrast, disruptions to the gut microbiota, such as a lack of microbial diversity or overgrowth of potentially pathogenic bacteria, can be linked to an increased chance of developing asthma (53, 54).

Children born by cesarean section are exposed to a higher chance of having asthma when compared to children by normal birth, which can be traced to the difference in their intestinal bacteria. A meta-analysis conducted in this area revealed that the risk of asthma was increased by 20% for those born by Caesarean section(55). Early childhood antibiotic usage was found to be linked to an increased likelihood of asthma, probably because of the variations in the gut microbiota.

Table 3: Overview of the Evidence on the Relationship between Antibiotic Exposure and the Risk of Asthma and Eczema

Study	**Design**	**Number of studies**	**Age range**	**Exposure**	**Effect Size**
Tsakok *et al.*, (2019)(56)	Meta-analysis	10 studies	0-25 months	Cumulative antibiotic use	Substantial dose-response association: In infancy, the likelihood of eczema increased by 7% for every additional round of antibiotics given (pooled OR 1.07, 95% CI 1.02-1.11).
Almqvist *et al.*, (2015)(57)	Retrospective cohort	87,500 sibling pairs	10-13 months	Any antibiotic prescription	Adjusted OR = 1.10 (95% CI: 1.03-1.18)
Marra *et al.*, (58) (2009)	Retrospective cohort	251,817	0-4 months	Any antibiotic prescription in the first year of life	Adjusted HR = 1.21 (95% CI: 1.08-1.16)

The evidence collected by means of data from various path breaking studies supporting the link between antibiotic exposure and early childhood asthma is shown in Table 2 . The effect sizes depict the strength and direction of the link. This association has been the subject of numerous studies. A substantial dose-response association seen between cumulative antibiotic use and the chance of developing eczema was observed after a meta-analysis of 10 researches, with a 7% higher risk, for each excess course of antimicrobials taken in the early years. According to two different retrospective cohort studies, one involving 87,500 sibling pairs and the other involving 251,817 children aged between 0-4 years, the use of antibiotics was linked to a 10% and 21%

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increased risk of developing asthma, respectively. These results indicate that early childhood exposure to antimicrobials may elevate the likelihood of developing asthma.

Environmental exposure and Microbiota on the Progression of Asthma

Environmental factors like exposure to allergens and air pollution are identified as factors responsible for the development and exacerbation of asthma (59). Increased prevalence of allergies can be linked to the surge in air pollution caused by industrialization and the widespread use of automobiles (59-63). Exposure to air pollution can cause epigenetic modifications in the immune system, particularly during foetal development and early childhood. Environment we understand, has a substantial role in the hindrance and management of allergic diseases (64-66). Although outdoor pollution is alarming, indoor air quality could have more impact on allergy susceptibility, as young children typically spend substantial amount of time indoors, and the concentration of indoor pollutants can be substantially higher than exterior pollutants (67-69).

Another notable study, conducted in China found that "traffic-related air pollution (TRAP)" was significantly linked with a higher risk of allergy and asthma like conditions in toddlers. Furthermore, the study also showed that the children having to bear with family stress as being more susceptible to asthma. It also indicated that boys were more prone to allergic symptoms than girls.(60). An amplified risk of asthma and allergies has been interconnected to higher exposure to traffic-related air pollution during childhood, according to a meta-analysis of cohort studies. Higher exposure to PM 2.5 and black carbon is linked to a higher likelihood of childhood asthma. Furthermore, increased exposure to PM 2.5 is related to an elevated risk of sensitization to allergens (70). However, to validate these findings, further research is required, involving long-term studies with consistent monitoring over time.

These environmental factors can influence the microbiota in the airways and gut, leading to dysbiosis and exacerbation of asthma symptoms (18, 71, 72). In order to better comprehend the progression of childhood asthma, it is crucial to grasp how environmental exposure and microbiota interact with one another. Prior research indicates exposure to air pollution from traffic may heighten the likelihood of children developing asthma. However, some bacterial strains, such as Prevotella, may provide a safeguarding effect (73, 74). A study by Durack *et al.,* (2018) identified an increased in the quantity of Proteobacteria and Firmicutes and simultaneously a decrease in the quantity of Bacteroidetes and Actinobacteria in asthmatic children (75). The study by Ege *et al.,* (2011) found that agriculture environment is linked with increased bacterial diversity which reduces the threat of asthma among children (76). Another notable study examined how childhood asthma and wheezing phenotypes are linked to "traffic-related air pollution (TRAP)." This study indicates early childhood exposure to TRAP is linked with both transient and recurrent asthma and wheezing patterns (77).

The study by Arrieta *et al.,* (2015) illustrates that the children identified to have abundance of a specific bacteria, were less prone to develop asthma despite high levels of air pollution (32). These findings underline the importance of the interplay between environmental exposures and the composition of microbiota in the development and progression of childhood asthma.

CONCLUSION

Childhood asthma is a respiratory disease becoming increasingly prevalent worldwide, its pathogenesis is complex and multifactorial. The interplay between microbiota, environmental allergens and host immunity plays a crucial part in the development and exacerbation of asthma symptoms. The evidence reviewed, suggests that dysbiosis of the airway microbiota can contribute to the onset of asthma and its progression. The exposure to environmental triggers like air pollution and allergens can alter the composition of airway microbiota leading to the progression of asthma.

A notable advantage of this review is its incorporation of research studies that have investigated different aspects of the microbiome and immune system in relation to childhood asthma, providing a more comprehensive understanding of the mechanisms involved. The review highlights the potential for targeted interventions such as probiotics, prebiotics, and immunomodulatory drugs to modulate the microbiome and improve asthma outcomes.

However, the review's limitations include the heterogeneity in study design, microbiome assessment techniques, and asthma phenotypes, making it difficult to draw definitive conclusions. Apart from this, the review has not considered broader environmental and social determinants of health, such as exposure to environmental pollutants and social factors like poverty that also contribute to development of asthma and its severity.

Despite these limitations, the evidence collected suggests that altering the microbial flora may be a promising approach for the prevention and management of childhood asthma. Further research is needed to determine the optimal timing, duration, and composition of such interventions, as well as the potential risks and benefits.

To conclude, pathogenesis of childhood asthma involves the interplay of microbiota, environmental allergens, host immunity and dysbiosis of the airway microbiota contributing to the onset of asthma and its progression. The inclusion of studies, investigating different aspects of the microbiome and immune system, highlighting the potential for targeted interventions are required to improve asthma outcomes. Further research is needed to fully comprehend and address the complex interplay between microbiota, environmental allergens, and host immunity in childhood asthma.

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Author Contribution:

Dr. Santhosh Kumar S.V conceptualized the study, designed the research methodology, collected and analyzed the data, and wrote the manuscript.

Dr. Mohan C.K and **Dr. Sisir P.R** supervised the research, provided critical feedback, and revised the manuscript for important intellectual content.

Dr. Abina Augustine contributed to data collection, analysis, and interpretation, and assisted in drafting the manuscript.

Dr. Sivaramyapragathi R.S contributed to data collection, literature review, and manuscript preparation.

All authors reviewed and approved the final version of the manuscript.